

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-922

CHEMISTRY REVIEW(S)

DEC 6 1999

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-922 CHEM.REVIEW #: 3 REVIEW DATE: December 6, 1999

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AZ	15-NOV-99	16-NOV-99	16-NOV-99

NAME & ADDRESS OF APPLICANT:

Bristol-Myers Squibb
Pharmaceutical Research Institute
100 Forest Avenue
Buffalo, New York 14213-1091

Donald J. Handley
Manager, Worldwide Regulatory Affairs
(716) 887-7794
Donald_Handley@ccmail.bms.com

DRUG PRODUCT NAME

<u>Proprietary:</u>	Solag� Topical Solution
<u>Nonproprietary/USAN:</u>	4-Hydroxyanisole/all-trans Retinoic Acid
<u>Code Names:</u>	BMS-181158/BMS-181159
<u>Chemical Type:</u>	1,4
<u>Therapeutic Class:</u>	S

PHARMACOLOGICAL CATEGORY/INDICATION:

Solar lentigines from chronic
sun exposure

DOSAGE FORM:

solution

STRENGTHS:

2% 4-hydroxyanisole/0.01% tretinoin

ROUTE OF ADMINISTRATION:

topical

DISPENSED:

X R OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a). 4-hydroxyanisole (4-HA):

USAN Name: None INN Name: Mequinol CAS Name: 4-methoxyphenol
CAS Number: 150-76-5 Molc. Formula: C₇H₈O₂ Molc. Wt: 124.14

b). tretinoin:

USAN Name: tretinoin INN Name: tretinoin

NDA 20-922

page 2 of 2

Bristol-Meyers Squibb

Solag  (2% 4-hydroxyanisole/0.01% tretinoin) Topical Solution

CAS Name: retinoic acid CAS Number: 302-79-4

Molecular Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.44 g/mol

Code Name: BMS-181159

SUPPORTING DOCUMENTS: Refer to previous reviews.

REMARKS/COMMENTS:

The purpose of the current submission was to acknowledge and/or agree to the draft labeling. However, during the elapsed time since an APPROVABLE letter was issued and arrival of this submission, one of the facility inspections had expired. Therefore, all facilities were re-submitted to the Office of Compliance. An overall recommendation of ACCEPTABLE was issued 03-DEC-99 for all facilities. The EER is attached.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is recommended for APPROVAL under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.

cc: Orig. NDA 20-922
HFD-540/Division File
HFD-540/Division Director
HFD-540/PM/FCross
HFD-540/MO/DCook
HFD-540/Pharm/ANostrandt
HFD-540/BioPharm/VTandon
HFD-805/Micro/PStinavage
HFD-540/Chemistry/WTimmer
HFD-540/ChemTmLdr/WHDeCamp
HFD-830/DD/CWChen
HFD-830/DDD/BDunn

filename:

/S/ 12/6/99

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DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-922 CHEM.REVIEW #: 2 REVIEW DATE: 12-MAR-98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AC	11-DEC-98	22-DEC-98	23-DEC-98
BZ	05-FEB-99	08-FEB-99	09-FEB-99
BC	08-JAN-99	21-JAN-99	21-JAN-99
BC	10-FEB-99	11-FEB-99	11-FEB-99
BL	05-FEB-99	08-FEB-99	08-FEB-99
NC	02-MAR-99	04-MAR-99	04-MAR-99
BL	05-MAR-99	08-MAR-99	08-MAR-99
BC	16-MAR-99	17-MAR-99	17-MAR-99

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb
Pharmaceutical Research Institute
100 Forest Avenue
Buffalo, New York 14213-1091

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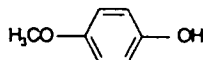
DRUG PRODUCT NAME

Proprietary: Solag  Topical Solution
Nonproprietary/USAN: 4-Hydroxyanisole/all-trans Retinoic Acid
Code Names: BMS-181158/BMS-181159
Chemical Type: 1,4
Therapeutic Class: S

PHARMACOLOGICAL CATEGORY/INDICATION: Solar lentigines from chronic sun exposure

DOSAGE FORM: solution
STRENGTHS: 2% 4-hydroxyanisole/0.01% tretinoin
ROUTE OF ADMINISTRATION: topical
DISPENSED: ☒ X ☐ R ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA,
MOLECULAR FORMULA, MOLECULAR WEIGHT:



a). 4-hydroxyanisole (4-HA):

USAN Name: None INN Name: Mequinol CAS Name: 4-methoxyphenol

CAS Number: 150-76-5 Molc. Formula: C₇H₈O₂ Molc. Wt: 124.14

NDA 20-922

Bristol-Meyers Squibb

Solagé (2% 4-hydroxyanisole/0.01% tretinoin) Topical Solution

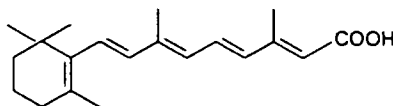
b). tretinoin:

USAN Name: tretinoin INN Name: tretinoin

CAS Name: retinoic acid CAS Number: 302-79-4

Molecular Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.44 g/mol

Code Name: BMS-181159



SUPPORTING DOCUMENTS:

DMF # [redacted] Type III DMF: Packaging components, [redacted]
[redacted] Letter of authorization dated
8-Dec-97. Date of last review: 3 Mar 99.

DMF # [redacted] Type III DMF: Packaging components, [redacted]
[redacted] Letter of authorization
dated 8-Dec-97. Date of last review: 11 Mar 99.

DMF [redacted] Type II DMF; 4-Hydroxyanisole; [redacted]
[redacted] Letter of authorization dated
17-Dec-97. Date of last review: May 1998.

DMF [redacted] Type II DMF: 4-Hydroxyanisole; [redacted]
Letter of authorization dated 9-Nov-98. Date of last
review: 17-Mar-99.

RELATED DOCUMENTS: None

CONSULTS: Labeling and Nomenclature committee.

REMARKS/COMMENTS: This NDA is recommended for APPROVABLE.
There is a Phase IV commitment and several
information requests.

NDA 20-922

Bristol-Meyers Squibb

Solag  (2% 4-hydroxyanisole/0.01% tretinoin) Topical Solution

CONCLUSIONS & RECOMMENDATIONS:

This NDA is found to be APPROVABLE under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.

cc: Orig. NDA 20-922
HFD-540/Division File
HFD-540/Division Director
HFD-540/PM/FCross
HFD-540/MO/DCook
HFD-540/Pharm/ANostrandt
HFD-540/BioPharm/VTandon
HFD-805/Micro/PStinavage
HFD-540/Chemistry/WTimmer
HFD-540/ChemTmLdr/WHDeCamp

/S/ 17/99

HFD-830/DD/CWChen
HFD-830/DDD/BDunn

filename:

APPEARS THIS WAY
ON ORIGINAL

NOV 13 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-922 CHEM.REVIEW #: 1 REVIEW DATE: 13-NOV-98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	30-DEC-97	31-DEC-97	04-JAN-98
BC	21-AUG-98	27-AUG-98	27-AUG-98
BC	18-SEP-98	30-SEP-98	31-SEP-98

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb
Pharmaceutical Research Institute
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DRUG PRODUCT NAME

<u>Proprietary</u> :	TRADENAME Topical Solution
<u>Nonproprietary/USAN</u> :	4-Hydroxyanisole/all-trans Retinoic Acid
<u>Code Names</u> :	BMS-181158/BMS-181159
<u>Chemical Type</u> :	1,4
<u>Therapeutic Class</u> :	S

PHARMACOLOGICAL CATEGORY/INDICATION: Solar lentigines from chronic sun exposure

DOSAGE FORM: solution

STRENGTHS: 2% 4-hydroxyanisole/0.01% tretinoin

ROUTE OF ADMINISTRATION: topical

DISPENSED: ☒ Rx ☐ OTC

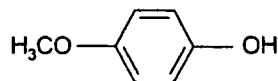
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a). 4-hydroxyanisole (4-HA):

USAN Name: None INN Name: Mequinol CAS Name: 4-methoxyphenol

CAS Number: 150-76-5 Molecular Formula: C₇H₈O₂

Molecular Weight: 124.14 g/mol Code Name: BMS 181158



NDA 20-922
Bristol-Meyers Squibb
TRADENAME Topical Solution
(2% 4-hydroxyanisole/0.01% tretinoin)

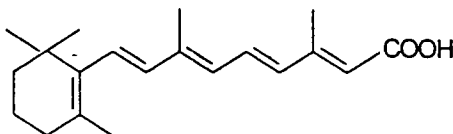
b). tretinoin:

USAN Name: tretinoin INN Name: tretinoin

CAS Name: retinoic acid CAS Number: 302-79-4

Molecular Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.44 g/mol

Code Name: BMS-181159



SUPPORTING DOCUMENTS:

IND [redacted] Depigmenting Solution, Bristol-Meyers Squibb
Pharmaceutical-Research Institute

DMF [redacted] Type II DMF; 4-Hydroxyanisole; [redacted]
[redacted] Letter of authorization dated
17-Dec-97. Date of last review: May 1998.

DMF [redacted] Type II DMF; Tretinoin; [redacted]
[redacted] Letter of authorization dated
21-Oct-97. Date of last review: August 1996.

DMF [redacted] Type II DMF: Packaging components; [redacted]
[redacted] Letter of authorization dated
8-Dec-97. Date of last review: 5 Nov 98.

DMF [redacted] Type II DMF: Packaging components; [redacted]
[redacted] Letter of authorization
dated 8-Dec-97. Date of last review: 2 Nov 98.

RELATED DOCUMENTS: None

PATENT STATUS:

Expiration date: U.S. Patent No. 5,194,247
16-March-2010
Patent Owner: Bristol-Myers Squibb Company
Type of patent: Composition and method of use

Expiration date: U.S. Patent No. 5,470,567
16-March-2010
Patent Owner: Bristol-Myers Squibb Company
Type of patent: Composition and method of use

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NDA 20-922
Bristol-Meyers Squibb
TRADENAME Topical Solution
(2% 4-hydroxyanisole/0.01% tretinoin)

Claim: composition and method of use of 2% 4-hydroxyanisole and 0.01% tretinoin in the treatment of hyperpigmentary disorders

CONSULTS: Labeling and Nomenclature committee: None; no tradename submitted.

REMARKS/COMMENTS: This NDA is recommended for NOT APPROVABLE. No DMF was submitted for the drug substance, and the DMFs for the container/closure system were deficient. The appropriate DMF holders were notified. In addition, overages of one drug substance were included in the final formulation without any justification. Submitted stability data were unacceptable. No labeling was submitted. ✓

CONCLUSIONS & RECOMMENDATIONS:

This NDA is found to be NOT APPROVABLE under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.

cc: Orig. NDA 20-922
HFD-540/Division File
HFD-540/Division Director
HFD-540/PM/FCross
HFD-540/MO/DCook
HFD-540/Pharm/ANostrandt
HFD-540/BioPharm/VTandon
HFD-805/Micro/PStinavage
HFD-540/Chemistry/WTimmer
HFD-540/ChemTmLdr/WHDeCamp

HFD-830/DD/CWChen
HFD-830/DDD/BDunn

/S/ 11/12/98

/S/

11/18/98 The deficient DMF for drug substance refers to the 4-hydroxyanisole, and not to the tretinoin.

filename: _____